<u>Emergency Use Authorization</u>: MVA Interagency Study Group (IASG) Current Thinking Regarding the Information Needed to Use Modified Vaccinia Ankara (MVA) Vaccines for Pre-exposure Prophylaxis in a Setting of Known Smallpox Virus Release – Including Prophylaxis of Individuals when Dryvax® is Contraindicated

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The following represents the MVA IASG's current thinking concerning the information needed to support the use of MVA vaccines under an Emergency Use Authorization (EUA) assuming other conditions found in the Project BioShield Act of 2004 are met. This document addresses the use of MVA vaccines for pre-exposure prophylaxis in a setting of known smallpox virus release and is intended for those persons that have not been exposed to smallpox following the event.

This document does not address the post-exposure use of MVA (i.e., for persons exposed to smallpox), which would need to be supported by a different set of clinical and animal studies.

Sponsors should be mindful that the EUA is an interim process, and sponsors should maintain focus on the appropriate path for licensure, which is not the primary objective of this document.

Sponsors should consult with CBER prior to initiating any studies that they intend to conduct in support of an EUA.

While we expect that a substantial safety and efficacy database to support large scale use of the vaccines under an EUA will be developed, we recognize that an event in which smallpox (variola virus) is used as a terrorist weapon could occur at any time and appropriate decisions would have to be made based upon the data available, including from other products.

To date, the MVA IASG has not been provided with any data that would indicate that MVA vaccines are sufficiently immunogenic in immunocompromised people to provide protection against smallpox. The IASG is aware of a recent animal study using severely immunocompromised monkeys that suggests that certain smallpox vaccines, namely MVA, NYVAC and Dryvax®, do not provide protection from a lethal monkeypox virus challenge.[1] With this in mind, the IASG strongly recommends that alternative prevention or treatment strategies be investigated for severely immunocompromised people at this time.

[1] Edghill-Smith, Y, *et. al.*, Smallpox vaccine does not protect macaques with AIDS from a lethal monkeypox virus challenge. *JID, 191:372-381*, 1 February 2005.

The MVA IASG has identified general types of data that would be needed to support use of MVA vaccines under an EUA. These include 1) animal safety and efficacy data, 2) human immunogenicity data, 3) human safety data, and 4) product data (i.e., manufacturing information and product characterization data). We have outlined below what will be needed in each of these categories.

These data represent what the IASG considers to be the minimum body of data needed to support the use of MVA vaccines for pre-exposure prophylaxis in an emergency under an EUA. The expected database needed to support the use of MVA under an EUA may change with time. The IASG considers the EUA requirements as a sliding scale, in that there will be a growing body of data to strengthen the scientific base and justification for use in an emergency. As additional supportive data become available, they should be added to the EUA data set.

Animal Efficacy Data

- *Which animal models are required?* No animal models using variola virus for the evaluation of smallpox vaccines have been developed. In addition, the technical hurdles for the use of variola virus (restriction to BL4 facilities at the CDC, need for WHO approval) make the development of an animal model using variola virus unlikely. The IASG believes that a combination of orthopoxvirus lethal challenge animal models provides the best approach to evaluate vaccine efficacy against human smallpox infection. The two most-studied animal models are the cynomolgus macaque (*Macaca fascicularis*) and the BALB/c mouse. Each model has certain advantages and disadvantages.

The monkeypox challenge model in cynomolgus macaques currently represents the best non-human primate model for an orthopoxvirus infection - the virus is often lethal with a pathogenesis similar to smallpox. However, working with monkeys presents technical challenges that limit the number of animals that realistically can be examined in a single study. Nonetheless, current MVA vaccine data using cynomolgus monkeys suggest that this model does provide a valuable tool for assessing MVA efficacy.

The BALB/c mouse model is commonly used in orthopoxvirus research. The orthopoxvirus disease pathogenesis and the elicited immune response are better understood in this model than in the non-human primate (NHP) model. Orthopoxviruses that are commonly used in respiratory lethal viral challenge studies include vaccinia, ectromelia, and cowpox. Viral challenge studies can be performed with sufficient numbers of mice to allow statistical analysis.

One well-designed GLP study in cynomolgus monkeys challenged with monkeypox by the intravenous or respiratory route could support the use of MVA under an EUA. The IASG expects that additional animal models, such as respiratory challenge data from BALB/c mice, will strengthen the scientific base and justification for use of MVA, as these data become available.

- *What challenge dose should be used in the experiments?* The challenge dose for the definitive efficacy study of the MVA vaccine candidate for both EUA and licensure purposes should cause severe measurable clinical disease and possibly death in unimmunized monkeys or mice. The dose required for the study will depend on the orthopoxvirus strain and route of challenge. Protection against a high challenge dose will increase confidence in the efficacy of the vaccine.

- *What is the appropriate route of challenge for the definitive study?* The normal route of human-to-human smallpox transmission is via the upper respiratory tract. Also, the most likely means of deliberate smallpox dispersal during a bioterrorism attack will be via an aerosol. Thus, respiratory challenge studies will better mimic the expected route of exposure. If the BALB/c mouse model is used, the respiratory route should be used for challenge. However, multiple routes of exposure, including intravenous and respiratory, have been investigated for the monkeypox NHP model, and could potentially generate data in the NHP model supportive of the EUA.

Suggested Definitive Animal Study for EUA: The EUA for MVA should be supported by a double-blind animal study that demonstrates efficacy (i.e., this may be a "modified" double-blind design such that the person who performs the clinical assessment does not know which vaccine was administered to which animal). Blinding of samples to be assayed should also be described. One acceptable approach is a monkeypox challenge study that closely follows the protocol described by Earl *et al*.[2]

In the NHP model, the study should have at least three randomized groups (additional groups may explore varying doses of MVA) of cynomolgus monkeys. Group 1 would receive MVA vaccination mimicking the proposed schedule for emergency use in humans. Group 2 would receive Dryvax® according to the licensed regimen as the positive control, and Group 3 would serve as an unimmunized control. All groups would be challenged with a lethal dose of monkeypox following the last vaccination. The clinical disease course and survival of the animals should be followed for 30 days post-challenge. All animals should be monitored closely with clinical observation and clinical pathology (including myocardial enzyme levels and viremia) during the study. In addition, any animal that dies or is euthanized should be necropsied and histopathology conducted.

In order for the experiment to be considered successful, there should be an obvious statistical difference between the animals in Group 1 (MVA recipients) and those in Group 3 (unimmunized controls), as defined by the "case definition" for severe clinical disease (see below). A prospective statistical analysis plan (with CBER concurrence) including endpoint definitions should be in place prior to the initiation of the pivotal study. The sample sizes should be determined by the expected differences and the justification included in the protocol.

[2] Earl, P. L., *et. al.* Immunogenicity of a highly attenuated MVA smallpox vaccine and protection against monkeypox. *Nature*, 428, 182-185, 11 March 2004.

Table1. Outline of Proposed Pivotal Study in Cynomolgus Monkeys

Group	Group Description
1	MVA (use the anticipated clinical dosing schedule under an EUA) See the Human Immunogenicity section for comments on the immune response.
2	Dryvax (given at time of last MVA vaccination)
3	Unimmunized (treated with placebo, i.e., saline)

All animals challenged with lethal dose of monkeypox after last vaccination

Primary Case Definition (monkeypox): Here is the case definition for severe clinical monkeypox, which will serve as the primary endpoint. The infected animal develops ≥100 non-resolving pox lesions during the duration of the study, and exhibits any two of the following clinical findings: 1) develop a body temperature of >103^{o}F, 2) exhibit >4% weight loss, or 3) appear listless/sluggish or moribund. In addition, any death due to monkeypox should be confirmed and counted. This case definition for severe clinical monkeypox virus infection may be used to evaluate efficacy of the vaccine by comparing clinical disease outcomes in vaccinated and unimmunized animals.

Secondary Case Definition (monkeypox): The infected animal should develop a pre-specified quantifiable number of pox lesions that will resolve during the duration of the study. Specific features of the secondary case definition(s) should also be pre-specified. This is the case definition for mild clinical monkeypox virus infection and may be used to differentiate between various MVA vaccines, thus providing a better understanding of the product.

If the mouse model is used, a virus challenge study with BALB/c mice should have a similar design to that outlined above for the NHP study (including a Dryvax arm), with more animals per group and a respiratory challenge using an appropriate orthopoxvirus. The sponsor should propose and justify clinical parameters in advance that would highlight differences between the vaccinated and control animals.

Before a definitive animal efficacy experiment for an EUA is conducted, preliminary animal studies, as well as clinical studies, need to be conducted in order to determine the optimal vaccine schedule and dose that has the best chance for success in humans. For example, the selected schedule and dose of MVA vaccine in humans should elicit a neutralizing antibody titer equivalent or higher than that induced by Dryvax (see “Human Immunogenicity Data”, below). In addition, sponsors should have completed adequate safety testing in immunocompromised animals prior to administration in immunocompromised people. The IASG encourages sponsors to determine the minimal immune response for protection; however, it is understood that the immunological correlates for protection of smallpox vaccines are currently not known.

Thus, in order to expedite the use of MVA under an EUA, determination of the minimal protective immune response is not required at this time.

For licensure of an MVA vaccine, and an indication for use in immunocompromised people, CBER may require that sponsors develop and conduct safety and efficacy studies in appropriate immunocompromised animal models.

Human Immunogenicity Data

Bridging the Animal and Healthy Human Host Immune Response: An important surrogate measurement for MVA efficacy is the magnitude of the elicited immune response after vaccination of animal and human subjects. The exact components of the immune response required for protection against smallpox are unknown. However, if the MVA elicited immune response is comparable to that of a vaccine previously known to be effective against smallpox (i.e., Dryvax®), this will increase confidence in the effectiveness of MVA, particularly since Dryvax can cross-protect across different orthopoxvirus species, and can thus serve as the common denominator. The most established measurement of the humoral response to vaccination is the plaque reduction neutralization test (PRNT) to vaccinia virus. Validated plaque reduction neutralization assays can be used to demonstrate that the geometric mean titer (GMT) of neutralizing antibody induced in healthy humans by the MVA vaccine is comparable to that induced by Dryvax® administered according to the recommendations in the approved package insert.

Neutralizing antibody titers from MVA and Dryvax® vaccinated people and animals will be required for EUA submission, since a comparison of the immune response between humans and those animals protected from challenge will help establish the efficacy of the vaccines. As already noted, it is important that the PRNT antibody titer induced by MVA be equivalent or higher than the response induced by Dryvax in both animals and humans (data generated by Earl *et. al*. indicates that is the case in monkeys immunized with two doses of a MVA vaccine). If the relative neutralizing antibody titer induced by MVA and Dryvax is significantly different in humans and animals, there are two options available to the sponsor: 1) the optimal schedule and dose of MVA in humans may have to be adjusted to produce a similar relative response to that which is protective in the animal model or 2) the dose of MVA can be titrated in animals to produce a similar relative response in humans, and then tested for efficacy in animals. In either case, sponsors should consult with CBER for guidance in advance of implementation.

In addition, supporting studies with non-validated assays such as plaque neutralization of variola virus and measurements of the cellular immune response to MVA are strongly encouraged for EUA purposes to support efficacy, but not required.

Individuals for whom Dryvax is Contraindicated:

Please refer to the following website which contains a link to the electronic package insert for Dryvax® and includes the complete list of populations for whom Dryvax® is contraindicated in non-emergency situations (http://www.fda.gov/cber/vaccine/smallpox.htm#lic).

The potential use for MVA includes a heterogeneous population including immuno-compromised persons and persons with other conditions, such as atopic dermatitis. Immunogenicity data should be obtained from such persons (see Safety Study, below), but, since this population will be contraindicated for Dryvax® in a non-emergency situation, a direct comparison of the immune response of MVA to that of Dryvax (as an indicator of efficacy) in these individuals will not be possible. In addition, validated animal models for each type of condition, that qualifies as a contraindication to smallpox vaccination, are presently not available. Overall, it may be difficult to reliably extrapolate safety and immunogencity data between the various subgroups within the larger Dryvax®-contraindicated population. The antibody level required to protect an HIV patient with a CD4 count greater than 350 /□L may be different from that required to protect an AIDS patient with a CD4 count less than 200 /□L. The severely immunocompromised patient may be unable to mount a protective immune response to vaccination. Such a patient may benefit from having their household contacts vaccinated with MVA, but ultimately may be better served with a product such as vaccinia immune globulin (VIG) or an antiviral drug to protect against smallpox.

For purposes of the EUA, to evaluate immunogenicity, we recommend testing the MVA product in populations such as those with atopic dermatitis and HIV patients with a CD4 counts greater than 350. It will be difficult to ascertain the level of immunogenicity that will protect these populations for whom Dryvax® is contraindicated. However, it will be informative to see whether these individuals can attain comparable immunogenicity to that seen in healthy adults vaccinated with MVA who achieve a level of seroprotection that correlated with seroprotection and survival in an adequate animal challenge model with vaccinia that included MVA and Dryvax®-arms. If the anticipated use of the vaccine includes other immunocompromised populations (e.g., persons with advanced HIV disease, certain cancers, immunosuppressive therapies, etc.), we recommend that immunogenicity data be obtained from these populations as well.

For MVA vaccine use under an EUA, it is required that immunogenicity data be obtained in vaccinia naïve persons. However, it will also be informative to have immunogenicity data in vaccinia experienced human subjects, but is not required for EUA submission at this time.

Human Safety Data in the Target Population

For emergency use of the vaccine, safety data should be obtained in vaccinia naïve humans given the same dose and schedule that would be used for pre-exposure prophylaxis. Using the sub-populations of HIV and atopic dermatitis patients as an example, The IASG suggests that 400 individuals be studied, distributed in four groups: 100 healthy subjects, 100 persons with a history of mild to moderate atopic dermatitis, 100 HIV infected persons with normal CD4+ counts, and 100 HIV infected persons with CD4+ counts in the 350-500 cells/μL range. HIV patients with CD4+ counts in the 200-350 cells/μL range should also be studied after the 350-500 cells/μL group is completed, and data from these individuals should be included in the EUA as they become available. However, the data in the individuals with CD4+ counts <350 cells/μL are not required for an initial EUA submission at this time. Decisions concerning the use of the vaccine in an emergency, however, could possibly be made with less data available.

In addition, if the anticipated use of the MVA product under the EUA includes other immunocompromised populations we recommend that safety data be obtained in these populations. It will also be helpful to have safety data in both vaccinia naïve and vaccinia experienced human subjects, however, data from the vaccinia experienced population is not required for EUA submission at this time.

Product Data (i.e., manufacturing information, product testing data and stability data)

Any material to be used under an EUA is expected to be manufactured according to cGMP (including source material) and should meet the lot release requirements for the vaccine. Storage parameters should be supported by stability studies and a stability protocol should be in place.